Non-Technical Abstract

A phase II/III, multi-center, open-label, randomized study to compare the effectiveness and safety of intralesional administration of RPR/INGN 201 in combination with Taxotere® and carboplatin and radiotherapy versus Taxotere® and carboplatin and radiotherapy alone in patients with locally advanced unresectable non small cell lung cancer (NSCLC)

Principal investigator: Stephen Swisher, M.D.

Lung cancer remains the worldwide leading cause of cancer deaths in both men and women. In the United States alone, an estimated 177,000 new cases were diagnosed and 158,700 deaths occurred in 1996. A type of lung cancer called "non-small-cell lung cancer" accounts for 8 out of 10 lung cancer cases. A small number of patients with late stage lung cancer (stage III) may be cured by combined treatments. Despite improvements in combined treatments in advanced NSCLC, most patients die because the treatments either do not work well enough at the cancer site treated, or fail to control the invisible cancer that is in other parts of the body at the time of treatment.

The primary objective of this protocol is to determine if injecting RPR/INGN 201 and using chemotherapy and radiation therapy improves the control of the treated and helps patients with lung cancer survive longer. This study will be set up to see if all three treatments, RPR/INGN 201, chemotherapy and radiation therapy work better than just chemotherapy and radiation therapy. The goal of the study is to show an improvement in the number of months the patients live. On average, patients with stage III lung cancer live for 15.5 months. This study will be considered successful if the length of time the patients live increases from 15.5 months to 19.4 months.

The study will be multi-center, the patients and doctors will know what treatment the patients are getting. Patients in this trial will have stage II or stage III non-small cell lung cancer that can not be operated on. Some patients will get injections of RPR/INGN 201 along with chemotherapy (using two chemo therapy drugs called Taxotere® and carboplatin) and radiation therapy, they will be in study treatment arm A. Some patients will get chemotherapy and radiation therapy alone, they will be in study treatment arm B.

Study treatment arm A: RPR /INGN 201 + Taxotere® + Carboplatin + Radiation Therapy

Study treatment arm B: Taxotere® + Carboplatin + Radiation Therapy

Treatment will be as follows for the investigational drug and the chemotherapy + radiation therapy:

- RPR/INGN 201 administration (Arm A only)

RPR/INGN 201 will be administered day 1, three days (± 1 day) before to the start of chemoradiation therapy (day 4) and on the first day of the third and fifth weeks of radiation therapy (day 18 and day 32).

RPR/INGN 201 will be given at a daily dose of 2×10^{12} vp as a mix with dextrose 5% water (D5W) adjusted to the biggest tumor. A single injection in the center of the accessible tumor will be administered for lesions ≤ 4 cm (3ml total volume) in largest diameter. For larger lesions, additional injection(s) will be given in a region of the tumor beyond the 4 cm radius and the final volume administered will be 10ml. The dose (2×10^{12} viral particles) and volume will remain unchanged during the treatment period.

RPR/INGN 201 will be delivered by fine needle injection either directly into the tumor by using a bronchoscope to reach the tumor, or into the tumor through the skin using CT scan guidance.

- Chemotherapy administration (both Arms)

Taxotere® will be given as a one hour IV infusion weekly at a dose of $20mg/m^2$ per day with carboplatin AUC-2 before radiation on days 4, 11, 18, 25, 32, 39 and 46 for a treatment duration of 6 1/2 weeks, with standard care according to local routine.

- Radiation Therapy (both Arms)

Radiation Therapy will be started on day 4 and administered at 2Gy daily five times a week for 6 and a half weeks for a total dose of 66 Gy.

Each patient will receive one course of treatment, and the patients' tumor will be biopsied at three months after the RPR/INGN 201 injections, chemotherapy and radiation therapy have ended.

This study is set up so that a statistical analysis will determine if it was successful. It is called a "randomized two arm study". Patients will be randomly entered into either arm A or arm B. The result will be based on evaluation of the tumor when it is biopsied and how long the patients survive. The statistical design is called "Baysian", it will allow the study to be completed with an answer to the question in a shorter period of time.

The study sponsor will look at the data collected at interim time points, 8, 12, and 18 months. Based on this analysis, it will be decided if there is any improvement when including the combination of RPR/INGN and if the trial should continue.

The number of patients required for this study is between a minimum of 160 and a maximum of 900, depending on the actual results of the local tumor control and patient survival (which is not known).

Under a conventional group sequential phase II to phase III design, using the same assumed margins of therapeutic effect, more patients would be required and the studies

would take longer. Under the proposed design, the study will last approximately 35 months.